REMARKS

I. Preliminary Remarks

Claims 10-24 are pending, of which claims 14 and 17-24 have been examined.

Support for the amendment to claim 20 may be found at page 49, lines 7-22, which discloses that a linker may be from 1-30 atoms long, and further describes that the linker may comprise amino acids.

II. Patentability Arguments

A. The Rejection under 35 U.S.C. §112, First paragraph

The rejection of claim 20 under 35 U.S.C. §112, first paragraph, as assertedly lacking written description for its recitation of a linker of from 5 to 30 amino acids is believed to be mooted by amendment of the claims to recite 1 to 30 atoms, as suggested by the Examiner.

B. The Rejection under 35 U.S.C. §103

Claims 14 and 17-24 were variously rejected under 35 U.S.C. §103, as assertedly unpatentable in view of Russell et al. (*Clinical Genetics*, 1999, 55:389-94, hereinafter "Russell") in view of Czekay et al. (*Mol Biol. Cell* 1999, 8:517-32, hereinafter "Czekay"), further in view of Blattler et al. (*Biochem*, 1985, 24:1517-24, hereinafter "Blattler"), in view of Davis et al (U.S. Patent 6,072,041, hereinafter "Davis"), further in view of Reddy (*Annals of Pharmacology* 2000, 34:915-23, hereinafter "Reddy"), further in view of White et al (U.S. Patent 5,962,266, hereinafter "White"), and further in view of Strom et al (U.S. Patent 6,165,476, hereinafter "Strom").

Applicants respectfully submit that the Examiner's rejection of the claims is based on a mistaken interpretation of Russell, and that a correct reading of Russell reveals that Applicant's invention solves a problem clearly identified by Russell. Russell is a general review that addresses a large number of diverse recombinant proteins that are not limited to lysosomal enzymes. See Table 2 at page 390. Contrary to the Examiner's statements, Russell does **not teach that there is difficulty in delivering lysosomal enzymes to the lysosome**; instead, Russell highlights the desirability of targeting specific **cell types, specific tissues or organ systems**. See page 390, bottom of 2nd col to page 391, top of 1st col.

For example, the Examiner's statement that Russell teaches at page 393 that lysosomal storage disorders are clear candidates for [fusion proteins] overlooks the immediately following statement at page 393 that the fusion proteins are needed to **target the recombinant lysosomal enzymes to the bone and CNS, not to the lysosome**:

> Lysosomal storage disorders are clear candidates for this therapeutic approach but much work is needed to adequately target the recombinant lysosomal enzymes to the bone and CNS. Page 393, 1st col.

As another example, the Examiner's statement that Russell teaches at page 390 that fusion proteins are needed to overcome the difficulties in delivering proteins to the intracellular region takes a general statement out of context and overlooks the immediately following statement at page 390, 2nd column that "**lysosomal enzymes can be effectively taken up and targeted to the lysosome of most cells**" due to the mannose-6-phosphate in the carbohydrate side chains (citing Pfeffer et al. "Targeting of proteins to the lysosome" *Curr Top Microbiol Immunol* 1991, 170:43-63)

Thus, nowhere in the cited portions of Russell does it say that there is a need to fuse lysosomal enzymes to proteins known to target the lysosome. One would not be motivated to fuse a therapeutic protein to a lysosome-targeting moiety when the therapeutic protein already enters the lysosome through another targeting mechanism and shows significant efficacy in treating disease. Thus, there is neither an explicit nor an implicit suggestion to combine Russell with the teachings of Czekay that RAP enters the lysosome.

Instead, Russell teaches that there is a need to target the specific tissues of bone and CNS, and Russell indicates that more work needs to be done in those areas. **Applicants' invention relates to the unexpected result of targeting the CNS using RAP fusions that cross the blood brain barrier** and thus fulfills this need identified by Russell. Russell thus highlights the **nonobviousness** of Applicants' invention.

Nothing in the art cited by the Examiner suggests that RAP would be useful in targeting the CNS or crossing the blood brain barrier. In contrast, Applicants' specification (Example III) at pages 67-68 shows that RAP is indeed taken up into the brain *in vivo*, that RAP crosses the blood brain barrier at a rate more than double the rate of transferrin (which was identified in Russell at p. 390, 1st col. as a potential CNS targeting protein), and that RAP enters the brain parenchyma (brain cells).

For the reasons described above, there is no suggestion or motivation to combine Russell with Czekay because Russell does not teach fusions of lysosomal enzymes with lysosome-targeting moieties, nor does Russell teach that targeting of lysosomal enzymes to the lysosome is a problem that needs to be solved. The other references cited by the Examiner do not remedy this deficiency. Furthermore, Applicants' invention provides unexpected results with respect to RAP fusions crossing the blood brain barrier and entering brain cells. Thus, the rejection of the pending claims as obvious may properly be withdrawn.

C. Double Patenting

The Examiner provisionally rejected claims 14, 17-20 and 22 under the doctrine of obviousness-type double patenting as unpatentable over claims 1-16 of co-pending, co-owned application No. 10/812,849, in view of Russell. Applicants submit that because application no. 10/812,849 has not yet even been examined, an actual double patenting rejection need not be entered. Both applications are assigned to the same Examiner, so the Examiner should know the status of both applications. If the Examiner believes that claims will issue in application no. 10/812,849 and that an actual double patenting rejection should be entered, Applicants will either amend the claims of application no. 10/812,849 to remove overlapping subject matter or file a terminal disclaimer to moot the rejection.

III. Conclusion

Applicants submit that all claims are in condition for allowance and request an early notification of the same. If the Examiner believes that further discussion would expedite allowance of the claims, he is earnestly invited to contact the undersigned at the number below.

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Respectfully submitted,

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